Bolar and experimental use exemptions in the EU: how the landscape has changed for generic and biotech drug makers

Manuel Campolini and Ignace Vernimme discuss the recent developments relating to both exemptions and consider what lies ahead.

During the 1990s, one of the hottest IP debates in the pharmaceutical arena was the introduction of a Bolar-type exemption in the EU.

A Bolar-type exemption primarily allows a generics company seeking regulatory approval for its product to conduct studies on a molecule that is still under patent without being considered as infringing that patent. The aim of this infringement exemption is to enable the generics manufacturer to launch its product on the market on day one following patent expiry. As a quid pro quo, the Hatch-Waxman Act granted the innovation industry a patent term extension to compensate for the loss of exclusivity as a result of the time lost between the start of the patent protection and the effective marketing of the pharmaceutical product.

The SPC, which was introduced in the EU in 1992 via Regulation No 1768/92, provides an extension of the protection that is comparable to that introduced by the Hatch-Waxman Act. However, the SPC was not accompanied by a Bolar-type exemption. And because none of the EU member states included such an exemption in their laws, pressure arose for the introduction of a Bolar-type exemption in the EU through generic industry lobbying and challenges before national courts.

The research exemption (or experimental use exemption), which was included in most national patent legislation and which grants infringement exemptions to third parties when the activities had the aim of gathering information for both research and commercial purposes, was often invoked before national courts to exempt Bolar-type activities conducted by generics companies. In parallel, and with the development of complex biotech products, innovative companies wanting to conduct experiments on molecules patented by other companies increasingly needed to clarify the scope of the research exemption. One question was whether the exemption could be invoked where the activities had the aim of gathering information for both research and commercial purposes, and if so, to what extent? However, the various national courts gave divergent decisions and failed to clarify the situation.

In 1998, the EU initiated a World Trade Organization dispute settlement procedure against Canada, a country where a Bolar-type exemption was in place but without any patent term extension. The EU argued that both the Canadian Bolar-type and drug stockpiling provisions were incompatible with the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). The panel set up to adjudicate the dispute found that while stockpiling was incompatible with TRIPS, the Bolar-type exemption was not.

Following these developments, case-law and the political landscape in the EU became much more favorable to the introduction of a Bolar exemption. In parallel, the European Court of Justice’s (ECJ) was interpreting the data exclusivity rules in such a way that was against the interest of the innovation industry.

Ultimately, a Bolar exemption was introduced in 2004 in Directive 2001/83/EC on medicinal products as a trade-off for new data exclusivity rules that were considered globally more favorable to the innovation industry. However, the wording and the scope of the directive’s Bolar exemption has been criticized for being unclear. In this context, what are the remaining uncertainties and what lies ahead?

### Bolar exemption

**Products covered**

The EU Bolar exemption is set out in Article 10.6 of Directive 2001/83/EC. It provides that:

- conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to [SPC].

To date, the Court of Justice of the European Union (CJEU) has not interpreted this provision. The EU Bolar exemption benefits primarily generic products, including those that use different salts, esters, ethers, isomers, mixtures of isomers, complexes, or derivatives with respect to the reference medicinal products (Article 10.2.b), and biosimilar products (Article 10.4). However, the exemption is not limited to generic and biosimilar products. It also covers tests and trials necessary to register:

- a medicinal product which does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product [Article 10.3].

Article 10.3 covers improved products that rely on a reference product and for which the applicant has submitted new data regarding the improvement in a so-called hybrid application (as opposed to abridged applications for standard generic products and full applications for new innovative products?). Some lawyers consider that this provision does not cover new innovative products since there is no reference product for these and, therefore, a full application based on Article 8 of Directive 2001/83/EC would be required. According to these lawyers, the activities described in Article 10.6 must – as a prerequisite – be related to an existing patented (reference) medicinal product in order for it to be covered by the Bolar exemption.

This calls for two observations. First, the various changes that can be made on the basis of Article 10.3 (e.g., change in the active substance, and/or new indication and/or new strength and/or new form and/or new route of administration) may result in the development of a truly innovative product that could be quite different from the reference product.

Second, the first part of Article 10.3, which refers to the registration of “a medicinal product which does not fall within the definition of a generic medicinal product”, is clearly an independent hypothesis from the rest of the paragraph (because of the use of the conjunction “or”). This hypothesis requires the submission of all appropriate pre-clinical tests and clinical trials, but it does not require – literally and logically – the existence of a reference product. Only the other hypotheses listed subsequently in the same Article 10.3 require – literally and logically – both the submission of pre-clinical tests/clinical trials and the existence of a reference medicinal product. These other hypotheses, together with the differences listed in Articles 10.4 and 10.2.b in relation to the use of different salts, esters, etc., cover basically all possible differences, improvements, etc., that can be made with respect to a reference medicinal product.
Therefore, it is only in the absence of its first part that Article 10.3 could have been interpreted as covering only the registration of medicinal products for which reference products exist. Yet, it is generally accepted that when a legal text is clear, it cannot be interpreted by adding requirements to it. In fact, the combined reading of Article 10.6 with the beginning of Article 10.3 does not exclude activities conducted by an innovative company on third-party-owned patents to generate all the data necessary for a registration despite the absence of any reference product. In such a situation, there should be a combined application of the beginning of Article 10.3 together with Article 10.6 and Article 8. The German transposition of the EU Bolar exemption specifies that all the activities needed to register any type of medicinal products, ie from standard generic products to truly new and innovative medicines, are exempt. The fact is that an exemption covering the registration of medicinal products for which no reference products exist promotes research and development and is valuable notably for innovative companies that are involved in the development of complex high-tech/biotech products.

**Activities covered**

Directive 2001/83/EC relates exclusively to the registration of medicinal products in the EU/EEA, so the exemption under Article 10.6 does not cover studies and trials whose use is for product registration outside the EU/EEA. The German transposition goes beyond the directive because the activities necessary for the registration of medicinal products outside the EU are also exempt. Italy, Denmark, and Spain (among other countries) transposed the directive in a similar way.

The UK and the Netherlands, on the other hand, are among those regions that have followed the wording of Directive 2001/83/EC closely. As a result, an issue has emerged that needs clarification. This issue relates to the situation in which studies/trials are conducted in the EU in order to make a first-stage registration of the product outside the EU and then later on within the EU (eg when there are differences in patent expiry or regimes). Would this first registration outside the EU disqualify the company from gaining the benefit of the Bolar exemption under Article 10.6? Logically, the EU Bolar exemption should be applicable. It appears that the Bolar exemption as introduced by Germany for instance avoids the arguments that might take place in other jurisdictions.

Another issue concerns the following questions: How does one determine the scope of the consequential practical requirements? Can the patented molecule that is needed to conduct the studies be manufactured by company 1 in country X, while the studies are conducted by company 2 in country Y, and can the registration be possibly obtained by company 3 for country Z? And in what quantities can the product be manufactured?

In a judgment rendered in December 2013, the Court of Appeal of Düsseldorf confirmed that advertising by a Polish manufacturer of active pharmaceutical ingredients (APIs) that offered a patented active substance for sale before patent/SPC expiry is not exempt. However, the court also considered that in its view, the sale, supply, and export (from Poland to Germany) of limited quantities of the substance to a generic company, allowing it to conduct the studies necessary to register the generic product, can benefit from the Bolar exemption. The court underlined that it is not possible for many generic companies to produce in-house all the active ingredients they want to sell. Therefore, it considered that a restrictive approach was not appropriate as it would render the Bolar exemption useless in many circumstances.

The court required the API supplier to take – on a case-by-case basis – precautionary measures to avoid the use of the substance for activities not covered by the exemption, eg the formulation of the substance into a final product that would be sold to the public. An in-depth analysis conducted by a well-known IP expert supports this view. Referring to a previous ruling of the Supreme Court of Poland in the same case, which excluded the benefit of the Bolar exemption, the same author pointed out that “the Supreme Court of Poland... has certainly misunderstood the Bolar rule and applied it in a manner quite different from the provision’s genuine role as explicitly formulated by the Community legislator.”

**Experimental use exemption (research exemption)**

Even if the wording of the various experimental use exemption provisions in the legislation of the different member states is generally very similar, the national courts have taken no uniform approach towards the scope of the provision. Of course, pure research is exempt, but what about mixed research that has a scientific aspect related to technological progress as well as a commercial component, eg the data generated by the research are required for the end-product registration? Should there be a distinction between pre-clinical research and Phases I, II, and III of the clinical studies to determine what is or could be exempt?

In Germany, the experimental use exemption is included in Part 1 §1 (2) of the German Patent Act, which states that:

**The rights conferred by the patent may not extend to acts done for experimental purposes relating to the subject matter of the patented invention.**

The two leading pieces of pharma case-law from 1995 and 1997, respectively, relate to biotech molecules. Basically, the German Bundesgerichtshof (a supreme court) considered that the trials did not infringe the patent despite the fact that they were also conducted with a view to obtaining a marketing authorization. The pre-requisite is that such activities must be carried out with the intention to gather new scientific knowledge about the subject of the invention, including its use, in order to overcome an existing uncertainty. Bioequivalence studies, stability testing, and other data required for submitting an abridged application for a standard generic product do not meet this requirement. However, clinical studies in relation to the registration of a biosimilar product may be covered by the exemption independently of Article 10.4 of Directive 2001/83/EC. Neither the existence (or non-existence) of a reference medicinal product nor the patentable (or non-patentable) character of the research at stake are relevant factors in applying for the research exemption. This position draws a relatively clear line, and the activities can even focus on product registration outside the EU on condition that the intention is also to gather scientific knowledge to overcome an existing uncertainty.

The Belgian situation appears to be quite similar to the German one. In 2005, Article 28§1 of the Belgian Patent Act was amended, and it now reads:

> The rights conferred by the patent may not extend to acts done for scientific purposes on and/or with the patented subject matter.

This amendment was integrated into a piece of legislation whose key aim was to promote biotech R&D in Belgium. During the parliamentary debate, the Belgian competent minister clarified expressly that this exemption would cover mixed activities that have both scientific and commercial components. The minister added that a more detailed provision would not be appropriate because should there be a legal dispute about it before a court, a broad interpretation of the exemption must prevail. He gave examples of mixed activities that are covered by the exemption: the development of a new application, of an improved therapeutic effect, of a more efficient formulation, of a new form of administration, and of a new indication. All examples are relevant for or even specific to the pharmaceutical sector. The results of the
parliamentary debate show that the explanation and declaration expressed by the minister were endorsed, and they should be the guideline for the Belgian courts.

In the UK, Section 60(5)(b) of the Patents Act 1977 exempts from patent infringement:

an act which […] (b) […] is done for experimental purposes relating to the subject-matter of the invention.

The wording is substantially the same as the German provision. However, English case-law has gone in a different direction. In the landmark decision in Monsanto Co v Stauffer Chemical Co, the court ruled that:

trials carried out in order to discover something unknown or to test a hypothesis or even in order to find out whether something which is known to work in specific conditions … will work in different conditions can fairly be regarded as experiments, but trials carried out … in order to amass information to satisfy … a regulatory body, that the product works as its maker claims are not … to be regarded as acts done for ‘experimental purposes’.

In Smith Kline & French Laboratories Ltd v Evans Medical Ltd, the court considered that:

what is or is not an experiment must depend upon the facts of each case but can include experiments designed with a commercial end in view.

It was, however, difficult to determine the precise borderline between activities that fall within and outside the scope of the experimental use exemption. And this leads to a greater legal uncertainty when compared with Germany’s approach.

The validity of the UK approach was questioned, and the UK Intellectual Property Office (UKIPO) took an initiative to change this situation. As a result, the UK implemented its research exemption provision in July 2014. The UKIPO introduced a guide in which it said that the research exemption will cover developments for the registration of a new indication for an existing medicinal product. It also confirmed that Bolar-type activities conducted in relation to generics, biosimilars, and any (innovative) products for their registration outside the EU are now covered by the revised UK research exemption. Also exempt are activities with a view to providing data that are necessary for health technology assessment (HTA) in the UK or elsewhere in the world, eg data to support assessment by the UK’s HTA, NICE. This provision entered into force on 1 October.

Convergences and differences between the two exemptions

Analysis shows that the EU Bolar and experimental use exemptions complement and overlap each other at the same time. While, the Bolar exemption applies primarily to activities that are needed to register generic products, ie activities that do not aim to gather new scientific knowledge, the normal prerequisite for seeking the benefit of a research exemption is to develop new scientific knowledge. However, the EU Bolar exemption also applies to activities that do aim to gather new scientific knowledge, such as clinical trials required for the development of a new indication as mentioned in Article 10.3 of Directive 2001/83/EC. In such a situation, the applicant for a marketing authorization may at the same time submit studies that are not considered to be a scientific progress (eg bioequivalence studies, stability tests, etc) and other studies that amount to a scientific progress (eg clinical studies in relation to a new indication). Both types of studies are covered by the EU Bolar exemption while the second type of study will also qualify for the experimental use exemption under the German and Belgian approaches, for instance.

Despite the fact that the plain wording of the beginning of Article 10.3 does not require the existence of a reference product and, therefore, studies to develop a new and innovative product can benefit from the Bolar exemption, the experimental use exemption remains necessary. The experimental use exemption would still apply to research that is not covered by the Bolar exemption, eg if the research is conducted without the objective of registration. In addition, this exemption remains relevant for other types of products and not just to medicinal (or veterinary) products. Incidentally, when the experimental use exemption covers studies that have a mixed objective, as in the situation allowed in Belgium, the use of such studies in order to obtain a marketing approval in a non-EU country should be exempt from infringement. And this would avoid the limitation inherent in a Bolar exemption covering only activities necessary for the registration of medicinal products within the EU.

Unified Patent Court

The ultimate objective is to have – after the transitional period following the entry into force of the European unitary patent system and the agreement on the Unified Patent Court – all European patents and related SPCs assessed by the UPC only, whether or not they have the same set of claims in the various member states. The UPC will then develop a harmonized interpretation covering all European patents and related SPCs and have a decisive influence on the future evolution of both exemptions.

The Bolar exemption included in Article 27(d) of the UPC agreement exempts the acts that are allowed under Article 10.6 of Directive 2001/83/EC, whereas the experimental use exemption included in Article 27(b) exempts acts that have been carried out for experimental purposes relating to the subject matter of the patented invention. It remains to be seen how studies designed to allow the registration of generic products outside the EU will still remain possible and, more generally, what interpretation will be given to the experimental use exemption.

Here, the UK’s alignment with the approach adopted by many EU countries is a sign to the UPC that a broad interpretation should be given to this exemption.

Conclusion

The trend in the EU to exempt scientific activities that have a commercial registration aim, as initiated by Germany in the 1990s, has grown significantly following the adoption in 2004 of an EU Bolar-type exemption to cover primarily standard generic products. In addition, an increasing number of member states have broadened the geographical scope of the EU Bolar exemption to cover generics registration within and outside the EU. This is not illogical as the benefit of the research exemption does not seem conditioned by a limitation in the use of the information resulting from this research that would prevent its use outside the EU for registration purposes.

Therefore, even if there is not yet complete harmonization of the situation in Europe, when confronted with a practical question that is not explicitly answered, one should bear in mind the above-described evolution, which could be summarized as follows:

• activities carried out before patent/SPC expiry with the intention to gather new scientific knowledge are normally exempt; and
• activities related to the production of scientific data required for product registration, even those with commercial aspects (eg sale of limited quantities of API to the research/generics organisations), before patent/SPC expiry are normally exempt; and
• other activities directly related to the marketing of a registered medicinal product to the public (eg manufacture, stockpiling, sale of the finished product) before patent/SPC expiry are normally prohibited.

References

1. Drug Price Competition and Patent Term Restoration Act (Public Law 98-417), 35 U.S.C. § 271(e)(1): “it shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented
invention… solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.”


3. Stockpiling is defined in Section 55.2(2) of the Canadian Patent Act as the manufacture and storage of articles intended for sale after the date on which the term of the patent expires.


5. Generics UK v Glaxo-BMS, judgment of the ECJ, 3 December 1998 in Case C-368/96.


7. Article 10(6) of Directive 2001/83/EC was introduced by Directive 2004/27/EC.

8. Hybrid application is a commonly used expression but which is not included in Directive 2001/83/EC, contrary to full, abridged and mixed applications (see Annex I of Directive 2001/83/EC).

9. The current Commission NTA (Volume 2A – Chapter 1 – June 2013, point S.3.2.2) suggests that Article 10(3) is limited to hybrid applications. However, the EC has rejected interpretations proposed from the NTA that were contrary to the wording of the provision at issue (see, for instance, judgment in case C-368/96 at point 47).

10. The availability of data exclusivity for such tests/studies is a separate issue, which is not examined herein (see for hybrid applications under Article 10(3)). M. Manley and M. Vickers “Shody European Commission policy is leaving pharma industry in the dark”, Scrip Regulatory Affairs, 7 July 2014.

11. German Patent Act, Part I § 1: The effects of a patent may not extend to: (a) studies and trials and the resulting practical requirements necessary for obtaining a marketing authorization to place a medicinal product on the market in the European Union or a marketing approval for a medicinal product in the Member States of the European Union or in third countries.

12. Other member states took the same approach, and a country such as Switzerland included in its Patent Act (Bundesgesetz über die Erfindungspatente – 232.14) Article 9 G which states that the effect of the patent does not extend to (c) acts required for obtaining a marketing authorization of a medicinal product in Switzerland or in a country with a comparable pharmaceutical control system.

13. Article 68.1a) of the Italian Patent Act (Codice della proprietà industriale) states that “[t]he exclusivity attributed by patent rights may not extend […] to acts […] aimed at obtaining a marketing authorization for a medicinal product, also in foreign countries, and to the consequent related practices, including the preparation and utilization of pharmacologically active raw materials strictly necessary for such purposes.

14. Section 3(3)(4) of the Danish Patent Act reads: “The exclusive right may not extend to […] actions which are restricted to the object of a patented invention which actions are necessary in order to get marketing authorization for a medicinal product for human or veterinary use in the EU in an EU Member State or in other countries.”

15. Article 52(1) of the Spanish Patent Act (Ley 11/1986 of 20 de marzo, de patentes de invención y modelos de utilidad) reads: “The rights conferred by the patent shall not extend to: (b) the studies and the tests carried out to obtain regulatory approval of generic drugs, either in Spain and abroad, and the subsequent practical requirements, including preparation, obtaining and use of the active principle for this purpose.”

16. Section 60(5)(b) of the (UK) Patent Act 1977 reads: “An act which, apart from this subsection, would constitute an infringement of a patent for an invention shall not do so if […] it consists of (i) an act done in conducting a study, test or trial which is necessary for and is conducted with a view to the application of… paragraphs 1 to 4 of article 10 of Directive 2001/83/EC, or (ii) any other act which is required for the purpose of the application of those paragraphs.”

17. Article 53.4 of the Dutch Patent Act (Akkoordwet van 15 December 1994) reads: “The carry-out of the necessary studies, tests and trials with the view of the application of article 10, paragraph 1 to 4, of Directive 2001/83/EC on the Community code relating to medicinal products for human use (OL J 311), and the practical requirements arising therefrom are not considered infringements of patents with regard to medicinal products for human use or veterinary medicinal products, respectively.”

18. Düsseldorf Higher Regional Court, Polpharma v Astellas Pharma, Case 1-2 U 68/13 of 5 December 2013. A request for a preliminary ruling addressed to the CJEU was withdrawn, and the case was removed from the CJEU register on 7 May 2014.

19. Strauss J., The Bolar exemption and the supply of patented active pharmaceutical ingredients to generic drug producers: an attempt to interpret Article 10(6) of Directive 2004/27, Journal of Intellectual Property Law & Practice, 2014, p 903, “considering the clear goal of the Bolar rule and having regard to the existing structure and functioning of the generic manufacturers in the Community, one should emphasize that, under the Bolar rule, no difference should be made between an applicant (or a marketing authorization, that has manufactured the API) acquired the necessary DAE, conducted the necessary studies, etc, and an applicant that acquired the API from a third source and has to rely on a letter of access”. Prof Strauss also stressed that any other interpretation “would be in clear contradiction of the genuine and declared goal of the Bolar rule.”


21. Joseph Strauss, op cit, p 905


24. RPC 1985, 515 CA.


(6D) For the purposes of subsection (5)(b), anything done in or for the purposes of a medicinal product assessment which would otherwise constitute an infringement of a patent for an invention is to be regarded as done for experimental purposes relating to the subject-matter of the invention.

(6E) In subsection (6D), “medicinal product assessment” means any testing, course of testing or other activity undertaken with a view to providing data for any of the following purposes – a. obtaining or varying an authorisation to sell or supply, or offer to sell or supply, a medicinal product (whether in the United Kingdom or elsewhere); b. complying with any regulatory requirement imposed (whether in the United Kingdom or elsewhere) in relation to such an authorisation; c. enabling a government or public authority (whether in the United Kingdom or elsewhere), or a person (whether in the United Kingdom or elsewhere) with functions of – (i) providing health care on behalf of such a government or public authority, or (ii) providing advice to, or on behalf of such a government or public authority about the provision of health care, to carry out an assessment of suitability of a medicinal product for human use for the purpose of determining whether to use it, or recommend its use, in the provision of health care.

(6G) In subsection (6E) and this subsubsection – “medicinal product” means a medicinal product for human use … (within the meaning given by article 1 of Directive 2001/83/EC(a).


29. Regulation (EU) No 1271/2012 of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection and Council regulation (EU) No 1260/2012 of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection with regard to the applicable translation arrangements.


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